PCT/EP2003/014432

5

Patent claims:

1. A process for the isolation

a) of the 3R,2'R stereoisomer of glycopyrronium bromide or iodide (formula II: A = Br or I),

10

or

b) of the 3S,2'S stereoisomer (formula IV: A = Br or I),

or

15

c) of the 3R,2'S stereoisomer of the thienyl analog of glycopyrronium (formula VI: A = Br or I),

or

d) of the 3S,2'R stereoisomer (formula VIII: A = Br or I),

$$\begin{array}{c} A^{-} \\ H_{3}C - \stackrel{\uparrow}{\underset{CH_{3}}{\bigvee}} \\ \end{array} \begin{array}{c} O \\ HO \end{array} \begin{array}{c} S \\ \end{array} \begin{array}{c} VIII \\ \end{array}$$

5 where

a) for the isolation of the 3R,2'R stereoisomer of glycopyrronium bromide or iodide (formula II: A = Br or I),

the diastereomer mixture consisting of the 3R,2'R isomer and 3R,2'S isomer (formula III)

or the diaster eomer mixture consisting of the 3R,2'R isomer and 3S,2'R isomer (formula IIIb)

or

5

the diaster eomer mixture consisting of the 3S,2'R isomer and 3S,2'S isomer (formula V)

or the diastereomer mixture consisting of the 3R,2'S isomer and 3S,2'S isomer (formula Vb)

or

5

c) for the isolation of the 3R,2'S stereoisomer of the thienyl analog of glycopyrronium (formula VI: A = Br or I),

the diastereomer mixture consisting of the 3R,2'S isomer and 3R,2'R isomer (formula VII)

or the diastereomer mixture consisting of the 3R,2'S isomer and 3S,2'S isomer (formula VIIb)

or

15

d) for the isolation of the 3S,2'R isomer (formula VIII: $A = Br \ or \ I$),

10

15

the diastereomer mixture consisting of the 3S,2'S isomer and 3S,2'R isomer (formula IX)

or the diastereomer mixture consisting of the 3S,2'R isomer and 3R,2'R isomer (formula IXb)

is used for the recrystallization and the stereoisomer to be isolated in each case is obtained in enriched form as a precipitate, a solvent enriching the stereoisomer to be isolated in each case in the precipitate being used, and/or

those tertiary, basic diastereomer mixtures are employed in the quaternization which lead to the abovementioned quaternary diastereomer mixtures, and the stereoisomer to be isolated in each case is obtained in enriched form as a precipitate after the reaction, a solvent enriching the



stereoisomer to be isolated in each case in the precipitate being used.

- 2. The process as claimed in claim 1, in which solvent having a water content is used which leads to only the desired diastereomer being obtained in crystalline form, while the other diastereomer remains in solution or is obtained as an oil.
- 10 3. The process as claimed in claim 1 or 2, in which in the quaternization to give said diastereomer mixtures of the quaternary salts a suitable solvent, such as, for example, isopropanol or acetone, is used and thus said stereoisomers are isolated in enriched form in the resulting precipitate.
 - 4. The process as claimed in claim 1, 2 or 3, in which a solvent in which the diastereomer mixture dissolves readily is used for the re-crystallization and a second solvent causing crystallization is added in order to bring about crystallization.
- 5. The process as claimed in claim 4, in which methanol and/or ethanol are/is preferably used for dissolving and crystallization is brought about using ethyl acetate and/or tert-butyl methyl ether.
- 6. The process as claimed in claim 1, 2 or 3, in which for the recrystallization the diastereomer mixture is dissolved in a heated solvent and crystallization takes place by cooling.
 - 7. The process as claimed in claim 6, in which the diastereomer mixture is dissolved at boiling heat in 2-

25

propanol or ethanol and crystallization takes place on cooling to room temperature or below.

- 8. The process as claimed in claims 1-7 preferably for the enrichment of the 3R,2'R isomer of glycopyrronium bromide.
- 9. The process as claimed in one of the preceding claims as a prepurification stage for obtaining a primary enrichment of diastereomers or, if enrichment has already taken place, to give a further increase in the diastereomer purity.
- 10. The process as claimed in one of the preceding claims, 15 solvents or solvent mixtures being used which preferably contain at least one solvent selected from the group consisting of branched and unbranched alcohols having a low molecular methanol, weight, such as ethanol, isopropanol, 1-propanol, tert-butanol, isobutanol, 20 butanol, and also acetone, butanone or aceto-nitrile.
 - 11. The process as claimed in one of the preceding claims, a solvent having a water content of preferably less than approximately 5%, even more preferably approximately 0.5-2%, most preferably approximately 1%, being used in the quaternization.
- 12. The process as claimed in one of the preceding claims, a solvent having a water content of preferably approximately 0.2-3%, more preferably approximately 0.5%, being used in the recrystallization.

Vienna, on 02.21.2005